Optimization and Comparison of Normal Tissue Complication Probability Models in Radiotherapy

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Jian ZHU[1,2,4,5], Antoine SIMON[1,2], Oscar ACOSTA[1,2], Gaël DREAN[1,2], Guillaume CAZOULAT[1,2], Caroline LAFOND[1,2,3], Khémara GNEP[3], Huazhong SHU[5,6], Limin LUO[5,6], Elisabeth LE PRISE[3], Pascal HAIGRON[1,2,6], Renaud DE CREVOISIER[1,2,3]

[1] INSERM, U 642, Rennes, F-35000, France;
[2] Université de Rennes 1, LTSI, Rennes, F-35000, France;
[3] Département de Radiothérapie, Centre Eugène Marquis, Rennes, F-35000, France;
[4] Department of Radiation Physics, Shandong Cancer Hospital and Institute, Jinan, PR China;
[5] Laboratory of Image Science and Technology, Southeast University, Nanjing, PR China;
[6] Centre de Recherche en Information Biomédicale sino-francais (LIA CRIBs)

Abstract −In the context of cancer radiotherapy, toxicity prediction is of the major importance to evaluate and compare dose plans. Normal tissue complication probability (NTCP) models are the major methods to predict and prevent the presentation of toxicities, but they have to be optimized and their predictive capacities have to be evaluated. In this investigation, the six main NTCP models were studied and their parameters were fitted on prostate cancer. The results argue that rectum toxicity within 2 years shows some characteristics of a serial organ (n=0.35). Poisson EUD and Logit EUD models have the better predictive abilities and their use in clinical routine should be studied in further works.

Keywords

Normal tissue complication probability (NTCP), prostate cancer, rectum toxicity, radiotherapy

I. INTRODUCTION

The aim of radiotherapy techniques is to maximize damage to the tumor while, at the same time, keeping complication to the surrounding normal tissues as little as possible. The prediction of radiation toxicity may have a direct impact on treatment planning because it enables to estimate, and therefore to compare, the toxicity induced by different dose plans. Nowadays, this toxicity prediction relies on toxicity models, called normal tissue complication probability (NTCP) models. They are based on Dose-Volume Histograms (DVH) representing the volume of structure receiving a dose greater than or equal to a given dose, and so summarizing 3D dose distributions. Six main NTCP models have been proposed since 1978. All of them are based on parameters that have to be optimized according to patient population follow-up databases. Some articles in the literature [1-3] have proposed optimized parameters values for one or more of these models, but none have already proposed to optimize the parameters for all of them and to compare them in order to determine the models having the most predictive values. The purpose of this investigation was to implement all the six models, to optimize their parameters in the context of rectum toxicity of prostate cancer and to determine which model(s) have the highest predictive value.

II. MATERIALS AND METHODS

II.1. Materials

The study included 188 patients having received 3D conformal radiotherapy for prostate carcinoma in the Radiation Department of the Eugene Marquis Center. The data were retrospectively collected and analyzed. Normal rectum DVHs were obtained for all 188 patients. The rectum toxicities were graded using the Radiation Therapy Oncology Group (RTOG) grading scale. Patients experiencing grade 2 or higher rectum bleeding toxicity within 2 years after radiotherapy were counted as events.

II.2. NTCP Models

Lyman-Kuture-Burman model:

The most widely used NTCP model is the "Lyman-Kuture-Burman (LKB) model" raised in 1991 [4]. It uses a probit function $\Phi(t)$ to describe the dose-response relationship for normal tissues at homogeneous radiation (Equ.1-3):

$$NTCP = \Phi(t) \qquad \text{Equ.1}$$

where:

$$t = \left(D - D_{50}(v)\right) \Big/ \left(m \cdot D_{50}(v)\right) \qquad \text{Equ.2}$$

$$D_{50}(v) = D_{50}(1) \cdot v^{-n} \qquad \text{Equ.3}$$

There are three parameters:

- $D_{50}(v)$, which represents the tolerance of the partial organ volume v, is the dose that causes 50% probability of injury;
- m which characterizes the steepness of the dose-response at $D_{50}(v)$;
- n which represents the volume effect. When n is close to 0, the volume effect is small and the organ is often called 'serial', like spinal-cord or rectum; if n is close to 1, the volume effect is large and the organ is 'parallel', like lung and kidney.

Logit EUD and Schultheiss model:

Both the "Logit EUD model" and "Schultheiss model" were raised by Schultheiss [5] in 1983. "Logit EUD model" is a logistic equation with equivalent uniform dose (EUD) DVH reduction method (Equ.4-5).

$$NTCP(D) = \frac{1}{1+\left(\frac{D_{50}}{D}\right)^{k}} \qquad \text{Equ.4}$$

where (D is EUD for partial inhomogeneous irradiation):

$$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n \qquad \text{Equ.5}$$

It has a simple form with parameter D_{50} and slope factor k. In order to calculate the inhomogeneous irradiation, parameter n is enrolled in the EUD equation as a volume effective factor. "Schultheiss model" is an integral probability model for inhomogeneous irradiation, which considers the whole organ as N sub-units that calculated by logistic equation（Equ.6-7）. So there are only two parameters: D_{50} and k for Schultheiss model.

$$NTCP(D,V) = 1 - \prod_{i=1}^{M}\left[1 - NTCP(D,V_{ref})\right]^{V/V_{ref}} \qquad \text{Equ.6}$$

where

$$NTCP(D,V_{ref}) = \left[1+\left(D_{50}/D\right)^{k}\right]^{-1} \qquad \text{Equ.7}$$

Poisson EUD and Kallman model:

Both the "Poisson EUD model" and "Kallman model" were raised by P. Källman [6] in 1992. "Poisson EUD model" is a Poisson equation with EUD DVH reduction method (Equ.8).

$$P(D) = 2^{-\exp\left(e\gamma\left(1-\frac{D}{D_{50}}\right)\right)} \qquad \text{Equ.8}$$

Poisson EUD and Kallman model have the same relationship to homogeneous and inhomogeneous irradiation as Logit EUD and Schultheiss models. But Kallman model has three parameters: D_{50}, slope factor γ and volume effective factor s (Equ.9).

$$NTCP = \left\{1 - \prod_{i=1}^{M}\left[1 - P(D_i)^s\right]^{\Delta v_i}\right\}^{\frac{1}{s}} \qquad \text{Equ.9}$$

Parallel model:

This model was raised by A. Jackson [7] in 1993. In this model, the organ is assumed to be composed of independent functional subunits (FSU) organized with a parallel architecture and the complication is produced only if a sufficiently large number of FSUs are destroyed. It is a probit formula with four parameters: $d_{1/2}$, which represents the dose at which 50% of the subunits are damaged; k, the slope parameter that determines the rate at which the probability of damaging subunits increases with dose $d_{1/2}$; And it is assumed that the cumulative functional reserve distribution can be described as a displaced error function and specified by the mean value of the functional reserve V_{50}, and the width of the functional reserve distribution σ_v (Equ.10-12).

$$NTCP = H(f) = \frac{1}{\sqrt{2\pi\sigma_v^2}}\int_0^f dv \exp\left[-\left(v - v_{50}\right)^2 \Big/ 2\sigma_v^2\right] \qquad \text{Equ.10}$$

where

$$f = \sum_i v_i p(d_i) \qquad \text{Equ.11}$$

Equ.12

$$p(d) = \frac{1}{\left[1+\left(d_{1/2}/d\right)^{k}\right]}$$

In this investigation, based on the discussion above, LKB, Logit EUD, Schultheiss, Poisson EUD, Kallman and Parallel models have been implemented and optimized by the fitting of their parameters for rectum toxicity of prostate carcinoma.

II.3. Models optimization and comparison

The parameters for each model were fitted by the Maximum Likelihood method [10]. For each patient i, no matter which model is used, the NTCP value can be presented by a function of its parameters and of the differential dose-volume bins like in Equ.13.

$$NTCP_i = F(Parameters; D_i, V_i) \qquad \text{Equ.13}$$

The log-likelihood equation L for the entire data set (all the patients) was then maximized over all feasible values. Let R_i=1 if the patient i experienced toxicity and R_i=0 otherwise, like Equ.14.

$$L(Cons\tan s; D_i, V_i) = \sum_i \left(\log(p_i)^{Ri} + \log(1-p_i)^{1-Ri}\right) \qquad \text{Equ.14}$$

The optimization process was coded and processed on Matlab software (The MathWorks, Inc.) with Exhaustive Optimization method. The optimization step is 0.01 for slope factors and volume effective factors, while 0.1 for D_{50} and $d_{1/2}$ (Unit: Gy). While we got the parameters for each model, we could calculate the NTCP values for each patient with each different model. Univariate analysis was performed to check the significant effect of each model in toxicity prediction. Multivariate analysis was performed using the backward procedure of the binary logistic

regression model containing all variables in univariate analysis.

III. RESULTS

Among the 188 patients, 13 patients (7%) developed grade 2 rectum toxicity and 6 patients (3%) grade 3. No higher grade was observed. Using the maximum likelihood method, parameters predicting $\geqslant$ grade 2 rectum toxicity of each model are shown in Tab.1

Model	TD (Gy)	n/s (Volume Effect Facotr)	m/k/γ (Slope Factor)	**Log-likelihood (LLH)**	**Univariate Analysis (*p*)**
LKB	70	0.35 (n)*	0.19 (m)	-58.24	0.043
Logit EUD	69	0.27 (n)	12.3 (k)	-58.40	0.057
Schultheiss	78	-	11.3 (k)	-59.32	0.054
Poisson EUD	70	0.27 (n)	2.50 (γ)	-57.96	0.045
Kallman	68	0.15 (s)	2.30 (γ)	-58.13	0.051
Parallel	$d_{1/2}$=80.6, k=4.39, V_{50}=0.3, σ=0.1			-58.63	0.073

Tab.1. Optimization results for each model and the *p* value from univariate analysis (* the character in brackets is the name of this parameter in the model)

Univariate analysis gave a group of p values without much difference. But multivariate analysis shown that, the most significant models of rectum toxicity prediction were Logit EUD (p=0.033) and Poisson EUD (p=0.027).

IV. DISCUSSION – CONCLUSION

In this work, we have optimized the parameters in six NTCP models and analyzed their predictive ability. Considering biological signification of the volume effect factor *n* of LKB model, the value of 0.35 suggests that rectum toxicity within 2 years may present some characteristics of a serial organ. Although the Logit EUD and Poisson EUD models have more simple mathematical form, they support more significant results in toxicity prediction. Källman has ever argued that only the Poisson equation has a strict radiobiological background since it is based on the Poisson statistical model of cell kill [6].

The parameters for each NTCP model will improve the optimization of dose distributing planning. The general inference drawn from our investigation is that the NTCP based objective functions will have advantages of needing only few number of parameters and allowing the radiation oncology physicist and physician to pay more attention on the biological effects for normal tissues.

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